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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,927	02/19/2002	David W. Smith		1842

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EXAMINER	
ANDERSON, REBECCA L	
ART UNIT	**PAPER NUMBER**
1626	

DATE MAILED: 10/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,927	SMITH ET AL.	
	Examiner	Art Unit	
	Rebecca L Anderson	1626	

-- The MAILING DATE of this communication appears on th cover sheet with th corr spondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 5-27 is/are pending in the application.

4a) Of the above claim(s) 7-19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 5,6 and 20-27 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 5-27 are currently pending in the instant application. Claims 1-4 were cancelled in the amendment filed 14 July 2003, claims 7-19 are withdrawn from further consideration as being drawn to non-elected subject matter and claims 5, 6 and 20-27 are rejected.

Election/Restrictions

Applicant's election of Group I in the paper filed 14 July 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the treatment (claim 23) and prevention (claim 25) of all disease conditions (claims 23 and 25) such as amyloid angiopathy, cerebral amyloid angiopathy, systemic amyloidosis, Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis of the Dutch type and Down's syndrome (claim 24).

The state of the prior art and the predictablility or lack thereof in the art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art

would recognize that in regards to therapeutic and preventive effects of all diseases, whether or not the disease is effected by the inhibition of cellular levels of amyloid β would make a difference.

It is the state of the art that there is no known cure or prevention for Alzheimer's disease and that there are only four medications available in the United States available to temporarily slow the early stages of Alzheimer's disease. The current drugs for the treatment of Alzheimer's disease, Aricept, Exelon, Reminyl and Cognex, treat early stages of Alzheimer's disease by delaying the breakdown of acetylcholine. Memantine, which blocks excess amounts of glutamate treats late stage Alzheimer's disease. (URL:http://www.cnn.com/2003/HEALTH/conditions/09/24/alzheimers.drug.ap/index.html).

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the inhibition of cellular levels of amyloid β, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 27 due to the unpredictability of the role of the inhibition of cellular levels of amylid β, and since the treatment of Alzheimer's disease is mediated by the breakdown of acetylcholine or the inhibition of excess amounts of glutamate.

The amount of direction or guidance present and the presence or absence of working examples

The only direction and guidance present in the specification is the suppression of amyloid precursor protein (APP) (page 2) for the inhibition of cellular production of amyloid β, found on pages 312-367. Page 350 and 359 show that some compounds of

the present invention are not active for the inhibition of cellular production of amyloid β. Besides the statement on page 10 of the instant specification, which states that APP is believed to be involved in numerous disease states. There is no correlation between the inhibition of cellular production of amyloid β with Alzheimer's disease or with all other disease conditions, i.e. the specification is silent and fails to provide guidance as to what diseases are mediated by the inhibition of cellular production of amyloid β.

The breadth of the claims

The breadth of the claims is the treatment of all diseases with the compound of claim 27 (claim 23), the treatment of amyloid angiopathy, cerebral amyloid angiopathy, systemic amyloidosis, Alzheimer's disease, hereditary cerebral hemorrhage with amyloidosis of the Dutch type and Down's syndrome (claim 24) and the prevention of all diseases with the compound of claim 27 (claim 25).

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of all diseases would be benefited by the inhibition of amyloid β and would furthermore then have to determine which of the claimed compounds would provide treatment of the disease.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to

determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 27 for the treatment of any disease. As a result necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of claim 27 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

This rejection can be overcome deleting the claims.

Claims 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of proteolytic cleavage of amyloid beta precursor protein does not reasonably provide enablement for the modulating of the level of amyloid beta precursor protein, either by increasing or decreasing. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the modulating of the level of Amyloid Beta Precursor Protein (APP) (claim 21), specifically APP751, APP695wt, APP670/671, APP670/671/717, sAPP, α-sAPP or β-sAPP (claim 22) with the compound of claim 27.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic or preventive regimen on its face. It is noted that on page 1 of the instant specification it is stated that there is a continuing

need in the art for compounds that can specifically inhibit proteolytic cleabage of APP, thereby inhibiting amyloid β protein production.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to the suppression of cellular levels of amyloid β, whether or not Amyloid Beta Precursor Protein was increased or decreases would make a difference as to how and if amyloid β could be suppressed.

The amount of direction or guidance present and the presence or absence of working examples.

The amount of direction or guidance present is found on pages 312-367 wherein the suppression of cellular levels of amyloid β by the compounds of the formula as found in claim 27. There is no direction or guidance for the increase or decrease of Amyloid Beta Precursor Protein. The only guidance present is for the inhibition of proteolytic cleavage of APP.

The breadth of the claims

The breadth of the claims is the modulation (increase or decrease) of Amyloid Beta Precursor Protein with the compound of claim 27.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which compounds of claim 27 increase Amyloid Beta Precursor Protein and which compounds decrease Amyloid Beta Precursor Protein and how this would effect the inhibition of proteolytic cleavage of amyloid β.

The level of the skill in the art.

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity.

Thus, the specification fails to provide sufficient support of the broad use "modulating" the level of Amyloid Beta Precursor Protein with the compound of the claim 27. As a result necessitating one of skill to perform an exhaustive search for which compounds of claim 27 would suppress (inhibit the proteolytic cleavage of APP) and which compounds would increase the level of Amyloid Beta Precursor Protein.

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

It is suggested that these claims be amended to include only the inhibition of the proteolytic cleavage of APP instead of modulating.

Claim 26 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, the specification states "Aβ" on page 311, but does not provide a definition of this abbreviation in the specification or the instant claims. It is suggested that applicant cancel claim 26.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 26 claims a method for treating a subject in need thereof to decrease production of Aβ. However, the abbreviation "Aβ" is not defined in the specification or in the instant claims. Page 311 states "Aβ" but does not define the abbreviation in any manner. Therefore, claim 26 is indefinite because it is unclear what production is being decreased in the method. It is suggested that applicant cancel claim 26.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27, 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by NEGISHI ET AL. which discloses the basic cleavages of arylsulfonamides. NEGISHI ET AL. discloses on page 45, the compound of the formula X which corresponds to applicants instantly claimed compound wherein D is hydrogen, E is unsubstituted phenyl, G is unsubstituted phenyl and J is unsubstituted phenyl.

Claims 27 and 5 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by LINFIELD ET AL. which discloses antibacterially active substituted anilides of carboxylic and sulfonic acids. LINFIELD ET AL. discloses the compound 105, page 1743 in Table IV wherein Ar1 is 4-(n-C3H7)C6H4, R is 4-ClC6H4CH2 and Ar2 is 3,4-Cl2C6H3 which corresponds to applicants instantly claimed invention wherein D is hydrogen, E is phenyl substituted with halogen (chlorine), G is phenyl substituted with a halogen (chlorine) and J is phenyl substituted with alkyl (n-propyl).

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (703) 605-1157. Mrs. Anderson can normally be reached Monday through Friday 7:00AM to 3:30PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph McKane, can be reached at (703) 308-4537.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone numbers are (703) 308-1235 and (703) 308-0196.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45AM to 4:45PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4242, (703) 305-3592, and (703) 305-3014.

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